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RADIUM

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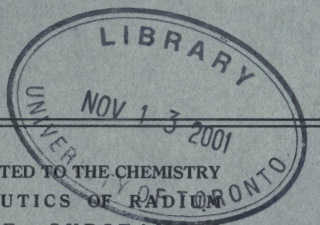
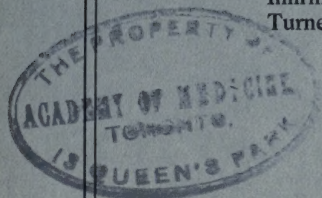
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A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY
PHYSICS AND THERAPEUTICS OF RADIUM
AND RADIO-ACTIVE SUBSTANCES

RADIUM

A MONTHLY JOURNAL DEVOTED TO THE CHEMISTRY, PHYSICS AND THERAPEUTICS OF RADIUM AND RADIO-ACTIVE SUBSTANCES.

Edited and Published by Charles H. Viol, Ph. D., and William H. Cameron, M. D.,
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VOL. V.

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RADIUM AND MESOTHORIUM IN UTERINE CANCER*

BY HENRY SCHMITZ, A. M., M. D., CHICAGO.

In 1879, Sir W. Crookes discovered the cathode rays. He exhausted the air of a glass tube more completely than had ever been done before, bringing down the pressure of the contained air to about one-millionth of an atmosphere, practically a vacuum. He then forced a current of electricity through the tube and made the discovery that the current was transmitted through the tube as a shower of extremely minute particles which, starting from the negative pole or cathode, traveled in straight lines and caused a beautiful fluorescent glow on the glass walls facing them. Crookes called these flying electrified articles "the cathode stream." We now know that these tiny particles are electrons.

In Germany, in 1895, Professor Röntgen made the memorable discovery of the X-rays. He found if the cathode stream be projected on to a solid body within a Crookes tube a vibration of great frequency is produced in this body giving rise to a radiation which is known as the X-rays. The extraordinary properties of the X-rays and their evident connection with the fluorescence of the glass of the X-ray tube led experimenters to study other phosphorescent bodies for the same type of radiation. In 1896, while studying the fluorescence of uranium, Henri Becquerel discovered radio-activity. In 1898, Schmidt found that thorium and its compounds were radio-active; and in 1900, Debierne found that actinium was also radio-active. But the most important discoveries were made by the Curies, in 1898, when they obtained radium from pitchblende, the substance being two million times more active than uranium. In 1907, Hahn discovered mesothorium. Radiotreatment experienced thereby an added stimulus, as the substitution of mesothorium for the rare and expensive mineral radium was made

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possible. Radio-activity is an atomic property observed in a few substances. Its elements liberate an energy which is characterized by the production of corpuscular and ethereal rays, heat, light, and electricity. The discharge of this energy is an essential property of the atom of the substance and results spontaneously; i.e., without extraneous cause.

At present, thirty radio-active elements are known. Three of these are gaseous: viz., radium emanation, thorium emanation, and actinium emanation. The others are solid bodies. The most important are those possessing the highest atomic weights: radium, 226.5, thorium, 232, and uranium, 239.

The radio-elements are divided into two large groups or families—uranium and thorium. The radio-active substances are found in nature in very minute quantities in the mineral deposits in which they and uranium are contained. These are chiefly pitchblende and carnotite for radium, and monazite for thorium. Radium is the only markedly radio-active element which has been obtained in its pure state.

Unchangeable radio-active elements do not exist, as each element undergoes in the course of time more or less rapid disintegration or decay. The elements of one family are related in the sense that one group, by the discharge of radio-active energy, is transformed into the other. The result of this transformation is the elements of an always lower and lower electropositive character are formed. (See Table I.)

The radio-active energy consists of a radiation consisting of three distinct kinds of rays which have been called by Rutherford α -, β - and γ -rays. By the discharge of α -rays, radium is gradually formed from uranium in the course of some thousands of years; radium emanation is formed from radium by a continuous giving off of α -particles, and from this, radium-A, -B, -C, -D, -E, and finally -F is derived. The more rapidly the transformation results, the greater is the penetrating power of the discharged α -particles and the greater the velocity of the β -rays. The emission of the α - and β -rays is coincident with a spontaneous liberation of electricity.

The duration of the life of the radio-elements varies from a few seconds to millions of years. By the half-period of radio-activity of a radio-element is meant the time required for the radio-activity to decrease to half value.

The α -rays are positive corpuscular rays or helium atoms with a positive charge. The discharge of each helium atom signifies a loss of atomic weight by the parent atom of four, which is the atomic weight of helium. This knowledge enables us to calculate the ultimate results of this disintegration—for instance, in radium. In the course of time, a radium atom gives off five α -rays—that is, five helium atoms; in other words, the atomic weight of radium, which is 226.5, is decreased by 5×4 or 20 in this transformation and we obtain as the end-product of radium a body whose atomic weight is $226.5 - 20$, or 206.5. The atomic weight of lead is 206.9. This simple arithmetical example shows that the precious radium is finally transformed into lead. A similar calculation demonstrates that thorium is finally converted into bismuth.

The β - or Becquerel-rays are negative corpuscular rays; viz., electrons. They are cathode rays existing in a natural state and are analogous to the rays which emanate from a cathode *in vacuo* and which, on striking a solid body, produce as secondary rays the X-rays. The β -rays are distinguished from the cathode rays appearing in cathode by the fact that they have a third greater velocity and therefore a larger penetrating power. The β -rays of one and the same substance do not

possess the same velocity, but possess different velocity groups, which, however, are characteristic of the substance. The degree of velocity determines the penetrating power of the rays. The γ -rays possess a considerably greater penetrating action than the X-rays; they never occur alone, but always in the company of the β -rays. The penetrating power of the γ -rays is about one hundred times greater than that of the hardest β -rays. It is impossible to take clear radiographs with the γ -rays, as they are absorbed very little more by the osseous than by the soft tissues. The penetrating power of the γ -rays of the different radio-active substances varies. The γ -rays, as well as the β -rays, produce secondary rays on striking a solid body.

An emanation is the direct product of decay of a radio-active element. A radium atom decomposes by the expulsion of an α -particle; i.e., a helium atom, leaving an atom of radium emanation. It is a gas which emits α -rays, and forms again into a solid body.

The amount of radium emanation in equilibrium with 1 gm. radium element is designated one curie. The volume of this amount of emanation is 0.6 cmm. The 1/1000 part of one curie is one millicurie. The content of radium emanation in different solutions is designated as mache units, referable to one liter of the dilution. One curie of emanation equals 2670 million mache units; this means that spring water of 2.67 million mache units activity contains in one liter the emanation which is in equilibrium with one milligram of radium.

The velocity, intensity, and penetrating power of the rays are of importance therapeutically.

The velocity of the α -rays is only one-tenth to one-twentieth of that of light. The velocity decreases rapidly with the distance from the source, and when the value of the velocity has sunk beneath a certain amount the α -rays lose certain properties which were present at the outset. This function of distance is known as *range*. The ray loses, for example, its photographic action, its fluorescence, and finally its ability to ionize gases; i.e., to make them conductors for the electric current when the latter passes through them. As the α -rays are atoms and possess a considerable size, they penetrate material bodies only with great difficulty. For instance, heavy glass or a thin metal plate are almost impenetrable to them. If α -rays act directly on the skin, they are absorbed in the most superficial layers and do not advance to any greater depths. During their absorption, they are probably capable of producing secondary rays, corresponding in this respect to the β -rays.

The behavior of the β -rays is entirely different. Their velocity is about the same as that of light; their intensity and penetrating power are markedly greater. The two kinds of β -rays, known as hard and soft rays, are of different penetrating powers. A piece of lead 3 mm. thick will absorb the β -rays. They are not only absorbed but also produce secondary rays which closely resemble the β -rays but have a very much reduced power of penetration.

The γ -rays pass through a lead plate 1 cm. thick. In fact, the γ -rays emitted by 30 mg. of radium bromide are capable of penetrating a steel plate 30 cm. thick.

When solid bodies, especially metals, are penetrated by rays from radio-active bodies, a new kind of ray is formed, which is analogous to the secondary X-rays which were discovered by Sagnac. α -rays are not capable of producing secondary rays; β -rays, on the contrary, produce very active secondary rays which are at times more powerful than the producing β -rays. The secondary rays are β -rays, but of a lesser velocity

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than their producers. They represent new electrons resulting from the absorption of the electrons which formed the primary rays. The X-rays, also, produce powerful secondary rays which are identical with β -rays.

The secondary rays produced by the same primary rays are more intensive, the denser the attacked metal. Eve and Townsend obtained the following numbers of the relative intensity of the secondary rays for different substances, produced by β - and γ -rays, -rays, and X-rays.

Substance	β - and γ -rays	γ -rays	X-rays
Lead.....	100	100	100
Copper.....	57	61	297
Brass.....	58	59	263
Zinc.....	57	..	282
Aluminum.....	30	30	25
Glass.....	31	35	31
Paraffin.....	12	20	125

TABLE I.

	Half-Time Period	Variety of Rays	Range of α -Rays in Air
Uranium 1.....	5 x 10 ⁸ years.....	Alpha.....	2.5 cm.
Uranium X1.....	24.6 days.....	Beta and gamma.....	..
(Uranium Y).....	(25 hours).....	(Beta).....	..
Uranium X2.....	1.15 minutes.....	Beta and gamma.....	..
Uranium 2.....	About 200,000,000 years.....	Alpha.....	2.9 cm.
Ionium.....	2 x 10 ⁸ years.....	Alpha.....	3.0 cm.
Radium.....	1,800 years.....	Alpha and beta.....	3.5 cm.
Radium emanation.....	3.85 days.....	Alpha.....	4.23 cm.
Radium A.....	3 minutes.....	Alpha.....	4.83 cm.
Radium B.....	26.7 minutes.....	Beta and gamma.....	..
Radium C.....	19.5 minutes.....	Beta.....	..
Radium C2.....	Fractions of a second.....	Alpha, beta, gamma.....	7.06 cm.
(Radium C1).....	(1.4 minutes).....	(Beta).....	..
Radium D.....	16.5 years.....	Very soft beta & gamma.....	..
Radium E.....	5 days.....	Beta.....	..
Radium F, or Polonium.....	136 days.....	Alpha.....	3.86 cm.
Lead?.....	..	..	..

Radium is the most important and the best known radio-active element. It is derived from ionium, a product of decay of uranium, and therefore occurs in all mineral deposits containing uranium. It belongs to the group of alkaline earths analogous to barium, with which it was first separated from pitchblende by Madame Curie. The atomic weight of radium is 226.5; the atomic weight of uranium is 238. If we subtract from the latter the α -rays or helium atoms, of which two are also given off from uranium2 and ionium, the atomic weight of radium is obtained: $238 - 3 \times 4 = 226$.

TABLE II. THORIUM.

	Half-Value Period	Variety of Ray	Intensity of α -Rays in Air
Thorium.....	1.3 x 10 ¹⁰ years.....	Alpha.....	2.72 cm.
Mesothorium I.....	5.5 years.....	..	..
Mesothorium II.....	3.2 hours.....	Beta and gamma.....	..
Radiothorium.....	2 years.....	Alpha.....	3.9 cm.
Thorium X.....	3.65 days.....	Alpha and beta.....	5.7 cm.
Emanation.....	53 seconds.....	Alpha.....	5.5 cm.
Thorium A.....	0.14 seconds.....	Alpha.....	..
Thorium B.....	10.6 hours.....	Beta and gamma.....	..
Thorium C.....	..	..	..
(C1+C2).....	60.5 minutes.....	Alpha and beta.....	5.0 and 8.6 cm.
Thorium D.....	3.1 hours.....	Beta and gamma.....	..

Thorium, the beginning member of the second family of radio-active elements, belongs to the rare earths, has an atomic weight of 232.4, and decreases to one-half its weight within 1,000 millions of years by the emission of α -rays. It is obtained from monazite found in Brazil. The immediate product of decay is mesothorium, with which we charge both mesothorium I and mesothorium II. The half-value period of mesothorium I is 5.5 years, that of mesothorium II, 6.2 hours. Mesothorium I is in equilibrium mesothorium II within a few days after its production.

Mesothorium I, in its chemical behavior, is identical with radium and is therefore obtained by a similar process. One thousand kg. of monazite give 2 to 2.5 mg. mesothorium bromide, while from 1,000 kg. pitchblende about 2 cg. radium bromide are obtained. Mesothorium always contains radium, which cannot be separated from the mesothorium. The percentage of radium in the combination is 25. The radio-activity of mesothorium increases at first, but within 3 years it reaches its maximum; it then decreases slowly and in about 10 years it reaches its half-value. The presence of radium, however, decreases the time of decay of radio-activity, so that 16 to 18 years pass by before the value of the radio-activity is one-half what it was at the time of the production of the mesothorium. Finally, if all the mesothorium should decay, the 25 per cent of radium would remain.

The radio-activity, and thereby the amount of radio-active substances, is determined by measuring the ionization which their rays produce. The electroscopic method is the simplest. The time which is necessary to produce a definite reduction in deflection can scarcely be measured; the stronger the rays are, the stronger must be the ionization and the more rapid the results of the discharge of the electroscope. The intensity of the radio-activity is under the same conditions inverse to the time of discharge. The electroscope must be constructed differently according to whether one desires to measure α -, β -, or γ -rays. γ -ray electroscopes must have walls of at least 3 mm. thickness of lead to positively exclude all β -rays. The standard of comparison is a known radium standard. All the important radio-active substances are measured according to known radium standards. This means that if the amount of mesothorium is 1 mg., the γ -rays of this mesothorium preparation produce the same ionization as 1 mg. radium bromide provided the conditions of the experiments are the same.

The α -rays have slight penetrating power and are absorbed at the surface of the body. The β -rays, representing free electrons and consisting of hard and soft rays, penetrate about 7 mm. into the tissues before they are completely absorbed. The γ -rays have the greatest penetrating power. Their coefficient of absorption by all substances is about 100 times less than that of the β -rays. The γ -rays, also, produce in the tissues in which they become absorbed, secondary rays mostly resembling the soft β -rays.

The biologic action of the different rays has been admirably studied and described by H. Dominici (8), of Paris, whose paper is herewith reviewed.

The application of 1 cg. of pure radium sulphate in a flat applicator of 4 sq. cm. to the skin of a healthy animal will produce within three weeks three varieties of changes distributed to three different zones of the body as follows:

1. A necrosis in the epidermis and cutis, the zone in which the greater part of the rays is absorbed; that is, all of the α - and soft β -rays.
2. An intense proliferation and retrogression to the embryonal

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state of the cells in the subcutaneous tissues and fascia. This zone has absorbed a smaller quantity of the rays than the preceding one; i.e., the medium β -rays.

3. Metabolic changes in the aponeuroses, muscles, and even the osseous tissues. The ultrapenetrating β - and γ -rays become absorbed in this zone.

Five or six weeks after the application of the radium, the epidermis and cutis resume their former state, while the other tissues do not return to normal for six to eight months.

This simple experiment shows—

1. The variety of the biologic action of the rays: necrosis, excitation of proliferation, embryonal retrogression, metabolic changes.

2. The connection which exists between the nature, intensity, and extent of the disturbances produced in the surface integument and the quantity of the rays absorbed by the skin in a given space of time; but it does not prove that these changes absolutely correspond to the absorption or amount of the rays. The susceptibility of organic tissues to change by the rays and the liability of animals and plants succumbing to the action of infectious agents is termed the receptivity or sensitization of cells.

This receptivity of organic tissues toward the rays depends under normal conditions, at least in part, on their age, which must be determined from their momentary phase of development as well as from the time of their formation in the organism to which they belong.

Therefore, cell elements which are in an embryonal or indifferent state—basal cells of the epithelium and the hair follicles, lymphoid cells, embryonal sex cells—are destroyed by an application of radium which would excite only a simple reaction or metabolic changes in the surrounding mature tissues. Thus cells of the hair papillæ, lymphoid cells, spermatozoa, and graafian follicles are killed by the rays, while the surrounding cells remain intact.

The receptivity of cells, however, depends not only on their age but on their species and the varieties of the latter in the same organism and on the accidental changes of a pathologic nature.

According to Danyasz, the differentiated elements of connective tissue are much less influenced by the ray than the adult cells of another species; for instance, those of the skin and mucous membrane. This difference in the behavior of the cells toward the rays is also found in their embryonal state, although their undifferentiated condition might imply the same receptivity.

The young cells of the basal layer of the epidermis perish much less readily than those of the papillæ of the hair follicles; they are different varieties of the same species.

Homologous elements are more or less receptive, depending on the age of the organism to which the cell elements belong. The tissues of the child are much more easily altered than the corresponding structures of the adult.

The influence of age and species or variety of species is further observable if the sensibility toward the rays is concerned with tissues pathologically changed by tumor formations or inflammatory processes, unless these pathologic processes change the receptivity of the cells, as they may alter their morphologic development and their nutrition.

Depending on their age, the following neoplasms belong to these radiosensitive tumors: ectodermal and basal-celled epitheliomata of Darrier and Krompecher, the morphologic structures of which resemble the basal layers of the epidermis; lymphadenomata, derived from em-

bryonal lymph-cells, which remain embryonal; sarcomata, which ordinarily proliferate from adult fixed connective-tissue cells (the latter reverting to their embryonal form after they have resorbed their products; i.e., connective-tissue fibrillæ and cartilaginous and osseous tissues); fibromata, whose fibroblasts are present in very large numbers and remain in their young state, instead of changing into adult fibroblasts and producing connective-tissue fibers.

On the other hand, squamous-celled epitheliomata, the cells of which grow with the formation of epithelial cones; fibrosarcomata; chondrosarcomata; osteosarcomata, the cells of which attain a relative maturity with the formation of fibers; cartilaginous and osseous substances; and fibromata with atrophic fibroblasts, which are found dispersed in small numbers in the extensive fibrous masses, remain refractory to the rays.

The law of age is apparently contradicted by certain tumors in which the embryonal cells are just as refractory as the adult cells, or in which the adult cells are just as sensitive as the embryonal elements. An example of the first instance is the tuberosus nevus, the retrogression of which is with difficulty attained in spite of radium and röntgen rays. The resistance toward radium is not only shown by the highest differentiated cells but also by those least developed which are refractory toward a ray otherwise capable of destroying embryonal cells. An example of the second category is represented by horny epitheliomata, fibrosarcomata, chondrosarcomata, and osteosarcomata, the receptivity of these being greater than that of most of the remaining tumors of the same varieties.

To conclude, the two great factors in the receptivity of tissues—age and origin—receive consideration in the development of the tumors; but their influence is often changed, diminished, or reversed by neoplastic processes which change the cells in such a manner that the latter conduct themselves as if they belonged to another species or variety.

Inflammatory processes also modify the receptivity of the tissues, for they destroy their growth and change their structure, thereby distorting the specific character of the tissues.

The resistance of the skin toward the destructive action of the rays is increased by many chronic inflammatory conditions, but it must be remembered that the relative immunization of the tissues against the necrotic action of the rays may be coincident with a sensitization of their stimulating, evolutive, and metabolic properties.

Therapeutic raying irritates but does not destroy the young granulating cells of torpid, badly cicatrizing wounds. It heals superficial or deep inflammatory processes, sparing the overlying skin. It atrophies keloids of the body surface, conserving the epidermis laying over them; for this reason, the cure of most of the inflammatory conditions which are amenable to radium treatment requires without exception a dose of rays which produces marked caustic effects.

Radium treatment is indicated in scrofulodermas but contra-indicated in most inflammatory lesions, in which weak rays that could kill neither the organic element nor the pathologic bacterium produce a retrogression and a cicatrization. The radium acts by changing the conditions of the affected area so that the latter becomes ill adapted as a nutritive media for the growth of pathogenic germs. This modification consists in a renovation of the chemical composition of the cells and the intracellular stroma.

The action of the rays on neoplastic tissue is of an impeding, destructive, or evolutionary character.

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The rays impede the growth of the diseased cells before they destroy them, so that the cessation of the growth of the tumor-cells always precedes the absorption of the tumor elements.

The destruction of these elements is either a direct or an indirect one. In the direct form, the tumor-cells become necrotic, their cytoplasm and nucleus disintegrate and dissolve without any change occurring in their morphologic structure. In the indirect form, a metamorphosis, which is comparable to that produced by the röntgen rays, precedes the cell absorption. The metamorphosis consists of a hypertrophy, often a gigantism of the nucleus, nucleolus, and even the centrosomes, which increase like pseudoparasites. The metamorphosis of tumor-cells is the sign of an abnormal development which the rays force upon them and which shortens the duration of their life, for very soon death of cells and absorption occur.

The evolutionary action of the radium produces a still more important process. It causes a retrogression of a part of the cells of the malignant tumors to their normal adult state. To understand the possibility of such a process, we must have a clear conception of the mechanism of the formation and growth of cancer-cells. The neoplasm deprives the cells of their function, especially that of becoming a part of the normal tissue layers. They become "strangers" to themselves and to the cells belonging to the same species and varieties. The growth is not only the result of the proliferation of a single cell group, but other cells also take part in this proliferation, which cells in the beginning were spared and which have gradually become included in the cancerous tumor.

The rays are capable of producing an effect directly opposite to the neoplastic process; i.e., they destroy the cells or inhibit their growth, but also return to them their prior normal function.

The therapeutic action of radium depends on the amount of radium used, the duration of exposure, and the kind and thickness of the filter. Radium rays destroy tumor-cells either directly or indirectly, as mentioned before; but finally the rays remove the tumor. However, we must make one presupposition: the rays really must reach the tumor with a sufficient intensity and the tumor must not have become disseminated by metastatic formations through distant parts of the body. Some cancers can be cured by a variety of methods, others not at all. The removal of the tumor does not mean the cure of the cancer, because the cure of a cancer signifies the death of all, absolutely all cancerous foci and cells present in the body. Therefore we must sharply distinguish between an anatomic and a clinical cure. In an anatomic cure a recurrence is impossible, because all the cancer-cells become destroyed if metastases are not present in the abdominal organs, ovaries, liver, etc. In a clinical cure the cancer has been improved only so far that clinically we cannot demonstrate anywhere the primary tumor and its metastases.

By the use of a correct filter technique the action of radium on tissues may be controlled, so that either α -, β -, γ -rays, or a combination of them, may attack the diseased area, as the action of α - and β -rays is only superficial; they may be dispensed with and only the deep penetrating hard β - and γ -rays used. For instance, a layer of cardboard will arrest the α -rays, while a pure lead filter of 3 mm. thickness will absorb all of the α -rays and the soft and medium β -rays. In gynecological work we do not use the α - and soft β -rays at all, and therefore always use a lead filter of 2 or 3 mm. thickness. The secondary rays which form in the filter are best absorbed by surrounding the metal filter with a cover of pure elastic rubber. Other substances which may be used as

filters are gold, silver, platinum, and brass—0.6 to 0.8 mm. gold, or 0.5 mm. platinum, or 2 to 3 mm. silver, or 3 to 4 mm. brass correspond to 2 to 3 mm. lead.

The dosage of radium is very important. A dense, heavy stream of rays emanating from radium or mesothorium contained in the smallest possible compact mass has a much more intensive action than the same amount of radium or mesothorium distributed over a large area.

Further, an entirely different result will be obtained from a large amount of radio-active substance applied at intervals for short periods of time than with a small amount of radium applied a correspondingly longer time. In other words, the action of 50 mg. of radium element for 100 hours; i.e., 5,000 milligram-hours is entirely different and more intense than the action of 5 milligrams of radium element for 1,000 hours. The same result cannot be obtained with a small amount by a longer continued exposure than can be obtained with a large amount within a correspondingly shorter period of time. Small doses stimulate growth and cause hypertrophy of tissues, while necrosis and death of cells can only result from the use of large doses. This fact is of practical importance. We stimulate the proliferation of a cancer and thereby render the patient worse by the use of small amounts of radio-active substances. However, a necrotization of the tumor and thereby a curative action is obtained only by the application of large amounts of rays. These facts correspond to those obtained by the use of the X-rays. Soft rays, in small amounts, stimulate the cancer to rapid proliferation, while a large amount of hard penetrating filtered rays applied within the shortest possible length of time have the opposite effect; that is, inhibition of growth and death of the cell. Foveau de Courmelles (9) uses 10 to 50 mg. of pure radium in monthly applications of 6 to 24 hours. Döderlein (16) precedes the treatment by an excochleation of the neoplasm, and then applies 100 to 150 or 200 mg. mesothorium until from 3,000 to 6,000 milligram-hours, and even 36,600, are used. He uses gold and lead filters. Jung (5) uses 100 mg. mesothorium in 2 mm. lead filters. With 30 to 36 mg. mesothorium, Kroemer (4) succeeded in changing the cancer tissue into a connective scar tissue free of any cancer-cells. Krönig uses up to 800 mg. mesothorium with heavy filters. He considers 200 mg. the minimum amount for a successful raying. Nahmmacher (30) obtained good and rapid results from the use of 30 to 100 mg. of radium. Pinch uses 50 to 100 mg. of radium filtered through a 2 mm. lead and a 3 mm. rubber filter. Each séance lasts 30 to 60 hours, given within 5 to 10 days. The applications are repeated every six weeks. Schauta claims that amounts above 100 mg. radium or mesothorium should not be used on account of the danger of latent formation of vesicovaginal or rectovaginal fistulæ. Sticker (3) uses amounts of 500 mg. or more. Smaller amounts do not penetrate sufficiently deep. He claims that mesothorium does not penetrate as deeply as radium. Wickham (23) has 19 centigrams of radium at his disposal and claims good result from about 2,000 milligram-hours' application, the radio-active substance being strongly filtered.

It is almost a settled fact that less than 50 milligrams of radium element or mesothorium of the same activity should not be used in gynecological work. It is deplorable that the different authors do not make it clear in their papers whether they mean to indicate the amounts used as being radium element or its salts. Ten mg. of radium element represent 17.076 mg. of RaBr_2 , or 13,138 mg. RaCl_2 , or 14.2 mg. of RaSO_4 or 12.655 mg. RaCO_3 ; in other words, 17.076 mg. RaBr_2 , or 13,138 mg. RaCl_2 , or

14.2 mg. Ra SO₄ have the same radio-activity as 10 mg. of radium element.

A qualitative difference in the clinical action of X-rays, radium or mesothorium rays does not exist essentially. They have the same curative action if used in the same amounts. The γ -rays are far superior to the X-rays in the intensity of penetrating action. This intensity is about 40 times stronger than that of the hardest X-rays. Clinical results coincide with this fact. The lesser intensity of the röntgen rays likewise cannot be overcome by an increased duration of their application.

The histologic changes which occur in the cancer tissue under the influence of the rays are as follows: During the first three weeks a hyperæmia and numerous typical and still more pronounced atypical mitoses are found. Then follows the metamorphosis characterized by an enlargement and vacuolization of the cancer-cells, retardation, and finally cessation of the division of the cell nucleus, then destruction of the nucleus and cell protoplasm, and, finally, destruction of the cells. There is a simultaneous new formation and increase of the connective tissue succeeded by a sclerosis and hyaline degeneration of the fibrillæ. On macroscopical examination of a piece of tissue, a narrow zone of necrotic tissue is seen on the surface, beneath this a layer of granulating tissue and degenerating cancer-cells, while in the deeper tissues areas of apparently normal and degenerated cancer-cells are seen. Whether these cells are capable of proliferation or are destined to perish cannot be proven on the microscopic examination. The destroyed cancer tissue is replaced by granulating or sclerotic, hyaline degenerated connective tissue. The musculature atrophies and disappears almost entirely. The blood-vessels show a hyaline degeneration of the adventitia and media. An obliteration of most of the blood-vessels is caused by a proliferation of the intima. The changes in the blood-vessels are considered by most authors as of great importance on account of the sudden disturbance of the nutrition of the tissues.

The changes in the objective condition of the patient caused by the use of radium or mesothorium are: (1) a restitution of the uterus to its former normal shape and form, (2) a disappearance of the infiltration in the parametria, and (3), a recurrence of the former normal movability of the uterus. In fact, an inoperable cancer is made operable within about 3 to 4 weeks by the use of 3,000 to 4,000 milligram-hours of radium or mesothorium.

The changes in the subjective condition of the patient correspond to the local action of radium. They are cessation of hæmorrhages and putrid discharges, disappearance of pain, improvement in the general condition of the patient; i.e., disappearance of the cachexia.

The primary action of radium in this disease is really beyond the fondest hopes of its most ardent supporters. By its use many sufferers may be given a new lease on life. This fact probably has led many a gynecologist to prematurely pronounce the radio-active treatment of cancer as curative, while it is only a symptomatic cure. It will take at least three more years of the most painstaking clinical observations before a final statement can be rendered.

In a few of the reported cases, a very late action of radiologic treatment on cancer has been reported. Döderlein (16) mentions the case of a patient who had been treated for four weeks with mesothorium without any apparent success. Six weeks afterward the patient appeared for an examination and was found to be completely cured. Metastases and cancerous foci lying more than 4 to 5 cm. distant from the radium capsule remain entirely unaffected by the radium. Others again—Freund,

Henkel, Krönig, Veit, and others—positively believe in a distant action of radium. The latter may be explained by the action of antibodies formed in the primary tumors by the action of the rays. They become absorbed by the blood stream, through which they are carried to the deep lying foci and metastases, where they act in a chemical manner. The chemotherapy of cancer is based on a similar supposition.

General disturbances of health observed during the raying are nervousness, headache, lassitude, loss of appetite, fever, albuminuria, stomach and bowel distress, vomiting, diarrhoea, pain in the bladder, rectal and vesical tenesmus.

Many authors support radium treatment with the application of large doses of hard X-rays to reach distantly lying metastases. Others combine with these intravenous injections of borcholin, colloid metals, to increase the action of the rays and thus decrease the time of exposure to the rays. Allmann (36), Krönig (20), Bickel (1), Opitz, Werner (40), and Ascher, recommend and use them. Thorium X, solutions of radium salts, have also been recommended for intravenous use to support the local action of the rays.

Prophylactic raying after operations to prevent recurrences is recommended by all the workers in this field. Gauss (7) reports 21 such cases, 20 of which have remained free of recurrences up to six years *post operationem*, while the usual percentage of recurrences after operations without radiologic treatment is sixty within the first year following the operation.

The question of whether inoperable cases of cancer of the uterus become operable after radium treatment is answered in the affirmative by some observers, while others deny it. This action, however, may be only an apparent one. Inflammatory and not cancerous infiltrations may disappear in the neighborhood of the cancer. However, Sigwart describes a case of inoperable uterine cancer in which a bulbous oedema of the entire base of the bladder disappeared after radium and mesothorium treatment. The carcinomatous cervix resumed its normal shape, and the case became operable. The disappearance of the bulbous oedema should prove the retrogression of the cancer. Franz considers the radium treatment of value in the purification of decaying cancers before operation and the rendering of inoperable cases operable by the disappearance of the infiltration. Wickham (23) claims the same results.

The action of radium on recurrent cancers is beneficial according to some observers, as Abbé, Grinsbaum, Latzko, and others, Abbé (11) reports a case which has remained free from recurrence for 8 years. Grinsbaum noted the disappearance of a recurrent cancer the size of a fist after a raying of 5 weeks. Werner, (40) Döderlein (16), Tate (22), and others state that recurrences are much more refractory to radium treatment than primary cancers.

The opinions of the treatment, its indications, and results reported by various authors will shed light on the value of radiologic treatment of cancer of the uterus. Krönig (12) mentions a case of an absolutely inoperable cancer in a woman who entered his clinic over two years ago in a desperate condition. She has not had any treatments for the last 18 months, has gained 30 pounds in weight, and has so far had no recurrences. Krönig (20) has had 27 cases of inoperable cancers of the uterus with a dissemination into the broad ligaments but without any metastases. These cases have been free from recurrences from 6 to 14 months and the patients have no subjective disturbances. Krönig is hopeful that some of the cases will not recur.

RADIUM

Radium therapy is especially successful in operable cases. Krönig (12) rayed seven such cases—all of them treated over six months ago. They have so far remained free from recurrence, while of three other cases which were subjected to a radical operation without subsequent prophylactic raying, one case already has had a severe recurrence. Krönig is inclined to believe that operable cases in particular should be subjected to the radium treatment, as the surgical treatment of cancer of the genital organs shows such bad results.

Recurrences are much less amenable to radium therapy than primary cancers; however, prophylactic rayings after radical operations are remarkably successful. Krönig has 20 cases which were rayed after a radical operation: 17 of the cases have been discharged from 18 to 36 months ago; 19 cases have remained free from any recurrences. If we consider that a recurrence after a surgical operation occurs under usual conditions within one year in 60 per cent of the cases, then we must call the above results remarkable at least.

Bumm (27) is of the opinion that radiotherapy produces in inoperable cases an improvement, in operable cancers a positive local cure. During the last year he has been using prophylactic raying after every radical operation—so far, with very good results. Of 108 cases of cancer, among 40 operable cases 15 have had recurrences. However, the time of observation has been too short to permit of a definite final opinion. Of 12 cases of cancer of the cervix which were held to be clinically cured in August, 1912, 2 having recurred; of 4 vaginal cancers, only 2 have recurred.

The penetrability of rays has been determined by microscopic examination of specimens obtained through operations or postmortem examinations. The destruction of the cancer-tissue and cancer-cells by the rays extended down 3 to 3.5 cm.; in a depth of 4 cm. viable cancer tissue was found in spite of the administration of large doses of the rays. Cancerous proliferations are usually not thicker than 1 to 2 cm. Proliferations deeper than 3 cm. are inoperable; therefore the success of radiotherapy is most remarkable.

During 1913, Döderlein (16) treated 153 cases of uterine cancer. Thirty-one of these cases are clinically well, subjectively as well as objectively. Of these 31 cases, 12 were so far advanced as to be inoperable; 24 cases have died; 93 are still under treatment; 11 have been discharged. One patient suffered from an inoperable cervical cancer with profuse hæmorrhages and ill-smelling discharges. She was so cachectic that her death was soon expected. She received altogether 11,630 milligram-hours of mesothorium during a period of three months. She has remained free from all subjective and objective symptoms for the last nine months. Cancer recurrences after radical operations are much more refractory to radiotherapy than primary cancers. Döderlein states that cancers of the female genitalia are more amenable to radium treatment than any other cancers. The reason for this is twofold: the cancers are much more accessible and the radium can be inserted into the cancerous mass, directly. Finally, strictures and contractions of the uterus and vagina are less objectionable than those occurring after radiotherapy in the rectum, bowel, or œsophagus.

Chéron and Duval (10) report 158 cases of vaginal and uterine cancer which they treated with radium during the last five years. This is a large and relatively long observed collection. Chéron and Duval lay great stress on the technique and do not deny that the bad results in many cases are due to faulty technique. The chief points in their technique are: (1) Inoperable cancers of the uterus and vagina must

be treated by Dominici's method of ultrapenetrating raying. (2) The ultrapenetrating method must be performed with the method of dosage inaugurated by Chéron and Duval. (3) The greater the amount of radium used, the greater the filtration must be. The value of radium treatment lies not only in the number of cures it may produce, but also in the remarkable improvements which can be obtained when all other therapeutic means are powerless. In the 158 cases there was one positive anatomical cure; 155 retrogressions, 93 of which were far reaching, and among the latter there were 46 clinical cures; only 2 cases were refractory.

Since September, 1911, Pinkus (48) has treated 38 cases of cancer among which were uterine and vaginal cancers, mammary, rectal, ovarian recurrences, cancers of the tongue and prostate. The superficial cancer nodules disappeared, but deep-reaching cancerous infiltrations remained uninfluenced. He obtained some very good results and concludes that radium treatment is indicated in operable cases in which the operation is difficult and therefore dangerous to life, as in advanced age, grave organic diseases, and all inoperable cases and recurrences. Prophylactic radium treatment after radical operation must be given for a long time to prevent recurrences. Among 38 cases, 9 clinical cures were reported. One patient with a cervical cancer has remained free from recurrence for 18 months. The lasting value of radium treatment in cancer must be admitted.

Schauta (50) treated 16 cases of cancer with massive doses. He had no success with small doses of radium or mesothorium. He rayed cases in which an operation was difficult or contra-indicated, the inoperable cases, and, prophylactically, all operated cases. His results as reported are 5 primary successes and 11 retrogressions.

Bickel (1) subjected 30 uterine, 19 mammary, and 14 rectal cancers to radium treatment. He had one clinical cure among the uterine cancers, 5 among the mammary, and one among the rectal.

Weinbrenner (37) reported the result obtained with radium in 32 cases of cancer of the uterus. He states that a local disappearance of the cancer can be obtained more successfully by radium than by any other means excepting surgical interference. He discusses especially the influence of radium on the healing of wounds following operations performed after raying of the cancer. Healing is usually not primary and a possibility of the formation of a fistula exists on account of a hyaline degeneration of the connective tissue. Of the 32 cases of cancer treated, 17 were uterine cancers, of which 6 cases were operable. Of the latter, 3 cases were clinically healed, 3 are still under treatment. Of the 11 inoperable cases, 3 are clinically cured, 5 markedly improved, 2 are still being treated, and one case was discharged as hopeless. Of the 9 recurring cancers, 2 are clinically healed, 5 improved, one discharged as hopeless, and one refused further treatment. Of 2 vaginal cancers one was discharged as cured. One ovarian cancer did not improve, one vulvar cancer also was refractory. Two cancers were treated prophylactically after a Wertheim operation.

Abbé (11) reports a case of cervical cancer, which was treated in 1905 after an excochleation with 60 mg. radium. The patient has remained well ever since. Abbé has had a number of inoperable cancers (cervical) which were treated by excochleation and radium and have remained well for the last 3 to 6 years.

Kroemer (4) treated 26 cases of cancer of the genital organs; of

these, 4 cases died and 17 were improved or are free from any disturbances. Eight of these cases were later operated on.

Jung (5) treated 4 cases with marked favorable results; i.e., clinical cures.

Wertheim (13) subjected 19 cases to radium and 3 cases to mesothorium treatment. Of the 19 cases, 9 were operable and 7 were afterward subjected to radical operations. The post-operative findings were: microscopically, 3 negative, 1 doubtful, and 3 positive; clinically, 6 good results and 1 negative result. Wertheim denies that any unusual benefit is derived from radium raying of inoperable cancer. He attributes the disappearance of the discharge and odor to the purifying action of radium. The three cases treated with mesothorium showed good clinical results, the microscopic examination showed one positive and one negative, while in the third case operation was refused.

Nahmmacher (30) deduces that operable tumors must be operated upon unless the operation is refused, and the operation must be followed by a prophylactic radium treatment. Inoperable tumors must be rayed immediately.

Foveau de Courmelles (9) states that radium and X-rays should not to be regarded as antagonistic to surgery but as its accessory means. Radium should be used only if an operation is refused by the patient or is contra-indicated, or if the cancer is inoperable. All operations for cancer, however, should be followed by a prophylactic radium and X-ray application.

In conclusion, we may summarize as follows:

1. The action of radium and mesothorium is probably the same.
2. The smallest amount used in treatment should be 50 mg. radium element.
3. The α - and soft β -rays must be excluded by a metal filter.
4. The secondary rays must be absorbed by a soft rubber capsule inclosing the metal filter.
5. The amount of milligram-hours varies from 3,000 to 6,000 or more.
6. The action of the rays should be supported by the X-rays.
7. Chemotherapy must be combined with radiotherapy.
8. Radiotherapy is indicated in (1) in inoperable cancers of the uterus, vulva, and vagina; (2) in operable cases where operation is refused or is otherwise impossible; (3) as a prophylactic to prevent recurrences after operations.
9. Contra-indications are: (1) advance of the "cancer disease," as multiple metastases and local extent, and (2) leucopænia of 3,000 or less and pronounced cachexia.

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RADIUM

ADVANCED EPITHELIOMA OF THE LOWER LIP. REPORT OF A CASE.

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The case we wish to report is that of a physician, aged 76 years, referred to us by Dr. J. B. Murphy, of Chicago, for radium treatment at the Western Pennsylvania Hospital, this city. It is of peculiar interest because of the prompt and most gratifying response to treatment with radium and of its satisfactory progress under our procedure of divided dosage. The result has been a pleasant surprise to all concerned, particularly so after the apparent failure of Roentgen ray treatment.

The history of the case to the date of admission, as given by the patient, follows:

"About seventeen years ago, what seemed to be a small pimple appeared on the mucous membrane of the lower lip, midway between the right corner of the mouth and the median line. This was pronounced by excellent authority to be an epithelioma and was treated by being curetted and cauterized under cocaine anesthesia and soon healed with no recurrence. During the summer of 1910 a similar growth appeared on the lower lip on the integument just inside and a little below the mucous membrane. This was also pronounced a malignant growth and treated in a similar manner with apparent success. It seemed to heal but a small dry scab still remained, scarcely perceptible and when removed left a perfectly dry surface underneath. It remained in this condition for several months when the small ulcer reappeared and was again treated in the same manner only much more energetically, the treatment being twice repeated at an interval of three months with the same apparent success. Operative measures were not advised lest they would perhaps spread the infection instead of obliterating it. In a few months the dry scab again appeared but remained quiescent till December, 1912, when the spot again broke out and rapidly assumed a malignant form, spreading slowly but surely over the entire lower lip despite all efforts to check it. A number of prominent specialists were consulted personally or by letter and every known remedy official and non-official that could possibly be of any avail was tried but to no purpose. In June, 1913, the Roentgen ray was tried, a high power water cooled tube being used and continued faithfully till late in October, 1914, when Dr. J. B. Murphy was consulted and advised radium as a last resort to try to save what little sound tissue remained, the lower lip and chin now being thoroughly fissured and honey-combed. For a long time previous the lesion had exhaled an offensive fetid odor."

When first seen by us, November 1st, 1914, the entire chin from angles of the mouth to the mental process and border of rami of jaw, both sides were involved in an ulcerating epitheliomatous mass, red, swollen, tender, presenting honey-combed appearance of various sized ulcers, discharging foul, irritating pus. Lower lip almost entirely destroyed, allowing saliva to dribble over chin. Thickening and induration of non-ulcerated soft parts and (apparently) of periosteum. This extended to submaxillary tissues and into left cheek about two finger breadths. Periosteum not exposed and superficial glands not enlarged to palpation.

Wasserman reaction—negative.

TREATMENT:

November 2nd—

108 milligrams radium element in four tubes of 27 milligrams each (in the form of sulphate) screened with 0.5 mm. silver and 2 mm. rubber, applied directly on surface of lesion at three different areas for one-half hour each,—one and one-half hours exposure.

November 3rd—

Same procedure with three tubes equaling 81 milligrams—two hours exposure.

November 4th, 5th, 6th, 9th, 11th and 14th—

Daily application of 54 milligrams radium element, screened with 0.5 mm. silver, 1.5 mm. lead and 1.5 mm. rubber, held on different areas over the entire surface from thirty to forty-five minutes each,—daily exposure being from one and one-half hours to two and one-half hours.

November 17th—

110 milligrams radium element applied as on November 2nd,—one and one-half hours.

The dosage, therefore, during this first period of treatment over sixteen days, totaled 1,200 milligram hours, in nine applications, averaging 72 milligrams radium element.

Improvement was noticed after second or third application; discharge less in amount and less offensive, and soreness less marked, except that the patient complained of burning sensation after treatment at part of surface which had previously been the site of the x-ray burn. Improvement continued slowly and uneventfully, except on November 12th there was a sudden and fairly severe hemorrhage from the ulcer at left angle of mouth.

Pronounced signs of beginning inflammatory reaction appeared on November 17th and patient was discharged for rest period. At this date there was little discharge, no odor, and healthy granulation of ulcers.

Readmitted February 13th, 1915. Ulcers appear entirely healed except a small sinus formation at right angle of mouth. Surface just below lip and left angle of mouth is irregularly covered with rough, berry-like, pea-sized or smaller excrescences, non-inflammatory and of nature of exuberant healthy granulations. Tissues throughout affected area thickened and slightly infiltrated. On margin of mandible 2.5 cm. left of median line is a small hard nodule. Still some swelling in soft part of cheek around left angle of mouth. Scar tissue at margin of lower lip appears tense, stretched. General appearance healthy. No pain, tenderness only at angles of mouth, no discharge, no odor. Patient feels fine.

TREATMENT:

February 13th—

25 milligrams radium element in tube, screened with 0.5 mm. silver and 1.0 mm. rubber applied on surface below right angle of mouth, one hour.

February 15th, 16th, 17th and 19th—

50 milligrams radium element in tubes, same screening, on right side, left side, left ramus of jaw and median line, for periods of one-half to two and one-half hours. Total dosage—563 milligram hours. Five applications averaging 50 milligrams radium element.

Discharged February 19th, with further improvement and signs of second reaction.

The condition on March 12th, in the patient's own words, is as follows:

"The lesion is practically healed, there being now only slight induration just below the left angle of the mouth and a small ulcerated spot near the right corner. Both, however, are rapidly disappearing. The orifice of the mouth, as might be expected, is much contracted, as well as the integument covering the chin. The beard on part involved is gone but the new tissue seems normal and healthy. To sum up, this case and its cure were certainly a wonderful and potent triumph for radium."

Later advice is that there is continued improvement and a softening and loosening of the tense scar tissue.

The diagnosis of epithelioma was not confirmed by us in the laboratory as it is our inflexible rule not to incise any suspicious growth before treatment.

REPORT ON THE RADIUM TREATMENT AT THE ROYAL INFIRMARY, EDINBURGH, DURING THE YEAR 1914.*

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Extra Medical Electrician to the Infirmary.

Sixty-three patients attended for radium treatment during the past year; of these, 36 were in-patients, 27 were out-patients; 34 of the patients suffered from, in all but 1 case, inoperable malignant disease, 23 of these from carcinoma, and 11 from sarcoma. There were 12 cases of rodent ulcer, 6 of exophthalmic goitre, 2 of otosclerosis, 1 of middle-ear deafness, 1 of Paget's disease, 1 recurrent wen, 1 simple tumour, 1 naevus, 1 leucoplakia, 1 warty tumour, 1 hypertrophied tonsils.

Though a cure was not effected in any of the malignant cases, nor, considering their advanced nature, was it to be expected, yet in practically all of those who were treated more or less benefit was produced by the relief of pain, the cessation of discharges, the healing of ulcerated surfaces, the removal of local growths and the prolongation of life. In some of the cases radium was used as a prophylactic after the surgical removal of a growth, and sufficient time has not yet elapsed to ascertain its effect. Remarkable results were produced in some of the malignant cases; thus

*British Medical Journal, Feb. 27, 1915, pp. 373-5.

an epitheliomatous growth was entirely removed, first from the posterior wall and then from the anterior wall of the vagina, so that not a trace of it remained; there has, however, been a recurrence which is being treated. In a rapidly growing periosteal sarcoma of the lower end of the femur in a boy of 13 the application of radium caused the growth to shrink and to become dense, hard, and fibrous, so that whereas, to use the words of the surgeon, Mr. Hodsdon, it bled like an aneurysm on the first introduction of radium; two months later, on a second introduction, it scarcely bled at all, and it was so hard and dense that it was only with difficulty that the radium could be inserted. This was an illustration of the well-known effect of radium in converting a sarcomatous growth into a fibrous one.

Malignant disease of the buccal cavity, the pharynx, larynx, and posterior nares appears to be less amenable to radium, but this may be partly due to the difficulty of administering a sufficient dose in such positions.

The beneficial effect of radium in rodent ulcer is now well recognized. Of the 12 cases treated during the year, 9 were easily cured; the remaining 3 have not yet been long enough under treatment for the effect to be produced. In each case the cosmetic result leaves no room for improvement. In small superficial rodent ulcers a single application may be sufficient; but it is important, in order to prevent a recurrence, that the deeper parts, as well as the superficial, should be adequately treated. Several of the cases had previously received, without sufficient benefit, applications of carbonic snow or large doses of the X-rays. Though this may render them, as the Radium Institute reports indicate, more refractory to radium, yet none have failed to yield to it.

In the 6 cases of exophthalmic goitre treated during the year, radium was of undoubted benefit, in 1 case apparently bringing about a definite cure. Its action consists in producing a sclerosis of the thyroid gland, following upon an obliterative endarteritis. As the treatment of this condition by radium was novel, great care was exercised in the earlier cases by giving small doses and keeping careful observation of the patients. Larger doses, which more rapidly produce a beneficial effect, are now administered. A diminution in the exophthalmos and tachycardia are amongst the first results to be observed.

SUMMARY OF CASES (EXCLUDING RODENT ULCER).

1. *Sarcoma* under the left eye. An advanced case, with abscesses and an opening into the antrum of Highmore. A dose of 2,280 mg.h. was given with temporary benefit.

2. *Recurrent epithelioma* following lupus in a male, age 41, recommended by Mr. Wallace. A growth affecting the region beneath the right ear was removed by Mr. Wallace, healed well, except a small patch, which healed after a dose of 240 mg.h. of radium. Five months later a recurrence occurred below, into which three tubes of radium were inserted, and removed after a dose of 5,040 mg.h. Six weeks later Mr. Wade reported a great improvement, the growth having practically disappeared. A few weeks later a recurrence occurred above, and radium treatment was given up.

3. *Sarcoma* of the scapula in a female, aged 29, recommended by Mr. Miles. Radium used prophylactically after surgical removal of the scapula, and inserted anteriorly. A dose of 360 mg.h. only was given, owing to the proximity of the subclavian vessels. Three weeks later a rapidly growing recurrence higher up, not where the radium had rested. Two tubes were inserted into the recurrence, and a dose of 2,520 mg.h.

given. A peculiar feature of this case was that the temperature of the patient always fell, and remained down during the radium applications. The radium relieved the patient's pain, which had been constant, but the patient rapidly sank.

4. *Recurrent scirrhus* in a female, aged 37, recommended by Mr. Miles. Breast removed in August, 1912. Some time afterwards a swelling began over the sternum. On admission on February 3rd, 1914, there was a large swelling over the sternum, measuring 3 by $2\frac{1}{2}$ in., and projecting about $1\frac{1}{2}$ in. A tube was introduced into the growth and radium applied externally in different positions, shielded by 1 mm. of silver. The dose amounted to 5,270 mg.h. Six months later the growth had disappeared. Photographs had been taken before and after treatment. Two months later two recurrences, one to the right, one above. A dose of 5,700 mg.h. was given, with the result that the swellings were markedly reduced. This patient has ceased to attend.

5. *Recurrent carcinoma* of the rectum in a female, aged 27. An aluminium tube containing radium was placed in a rubber tube and attached to a twisted silver wire. This was introduced so as to lie against the ulceration, and a dose of 1,030 mg.h. administered. Mr. Hodsdon considered that this treatment was beneficial, the induration became less, and pain was diminished. The patient went home, and has not since attended for more treatment.

6. *Epithelioma* of the lower jaw. It was large and unsuitable for radium treatment.

7. *Epithelioma* of the lower lip in a male, aged 55, recommended by Mr. Cathcart. The diseased area was about the size of a filbert nut; there was a crack in it above, but the mucous membrane was not invaded. A dose of 400 mg.h. was administered. Dismissed three weeks later greatly improved. Told to return in three weeks, but did not do so for many months, when the condition was so much worse that an operation had to be performed. The case was one which would probably have entirely yielded to radium had the treatment been persisted in.

8. *Secondary metastatic sarcoma* in a female, aged 27, recommended by Professor Alexis Thomson. Eight days after the growth had been removed from the back of the neck a tube of radium was introduced into the wound, and a dose of 960 mg.h. administered. A year later her family doctor, Dr. Genmell, wrote to say that he had examined her and could find no hardness or swelling near the cicatrix, and that she had made a marvellous recovery after we had expected her cure impossible.

9. *Epithelioma* of the vaginal walls in a patient of 40, recommended by Dr. Barbour. Duration some months; pain and watery discharge. There is a raised warty growth over upper two-thirds of posterior vaginal wall, also in anterior fornix. Microscopic examination shows it to consist of a squamous celled epithelioma. Operation inadvisable owing to risk of a rectal fistula. 15 mg. of radium protected by 1 mm. of silver fastened into a speculum and introduced so as to be in contact with the warty growth. A dose of 384 mg.h. was given. Six weeks later the patch was smaller and there was less discharge; 25 mg. of radium in an aluminium tube were attached to a pad protected on the upper surface by lead foil and placed in contact with the growth. A dose of 1,050 mg.h. was given. Some local peritonitis and lung trouble followed. In four months' time when the patient returned no trace of the disease could be found on the posterior vaginal wall, but there was

a decided plaque-like growth on the anterior wall. Twenty mg. of radium protected by silver, 1.3 mm. thick, were placed against the growth and left in, except for douching, for seven days, dose 3,200 mg.h. Six weeks later the growth had disappeared except for a trace in the anterior fornix. Two months later she returned with a hard lump on the anterior wall. The growth was rapidly increasing. By the application of 30 mg. of radium in aluminium, a dose of 5,060 mg.h. was given. At month later she returned complaining of pelvic pain, rectal discomfort and discharge. On examination under chloroform, the posterior vaginal wall, where the original growth had been, was found to be thickened, indurated, and grey coloured. The anterior wall presented the same appearance. Immediately below the cervix was a growth of the size of a gooseberry. The pathologist reported that this showed very extensive necrosis, so that it was impossible to recognize what the original tissue was. The patient is being kept under observation.

10. *Recurrent sarcoma* of the right orbit, growing rapidly and very vascular. A case of Dr. Sim's. A dose of 1,920 mg.h. was given, but the patient died a few days later with head symptoms.

11. A *scirrhus* of the left breast in a patient of 75, recommended by Mr. Caird. There was a hard tumour with an ulcerating crack and the glands were involved. To relieve pain a dose of 120 mg.h. in aluminium was given to the crack. The pain was relieved, and there was great local improvement. The patient ceased to attend.

12. *Fibro-sarcoma* of the right side of the neck in a man of 34, a patient of Mr. Struthers. Duration six years. Aching pain. Neck circumference, 17½ in. 20 mg. in aluminium inserted through an incision, and a dose of 5,400 mg.h. given. Six weeks later, growth no smaller, but more movable; pain removed. A large fresh deep incision showed a softened area where the tube had lain. Microscopically there were areas of necrosis round the positions in which the radium had been. By means of another tube a dose of 3,840 mg.h. was given. Considerable reaction with a discharging sinus followed. Four months later the growth was found to be much smaller and more moveable. The patient has ceased to attend.

13. *Myeloid sarcoma* of enormous size of the side of the face and back of the head in a man of 54, recommended by Mr. Dowden. As a palliative a dose of 3,360 mg.h. was given.

14. *Recurrent carcinoma recti* in a female of 54, recommended by Mr. Hodsdon. Previous operation a year ago; colotomy performed, rectum removed. Now a fistula into the vagina, constriction, tenderness, and pain. 20 mg. in aluminium introduced, and a dose of 3,840 mg.h. given. Considerable amelioration followed with relief of pain.

15. *Recurrent scirrhus* in a woman of 47, a patient of Mr. Caird. As the disease was very extensive the patient was recommended for X-ray treatment.

16. *Recurrent carcinoma* of bowel round a colostomy opening in a female of 41, recommended by Mr. Cathcart. Diabetic. A tube was inserted into the growth, but ulcerated out in three days. The patient died complaining of head symptoms.

17. *Sarcoma* of tonsils in a man of 50, recommended by Dr. Logan Turner. Four months' duration. Cannot open mouth much or swallow solids. An ulcerating mass chiefly on right side. 20 mg. in an aluminium capsule at the end of a rod were held for some eight hours a day by the patient close to, but not actually touching, the ulcer. After a dose

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of 1,310 mg.h. the patient ceased to attend. No beneficial effect, except that the ulcer appeared to get cleaner, was observed.

18. *Carcinoma* of cervix and vagina, advanced ulcerating, in a patient of 49, recommended by Mr. Brewis. 20 mg. in aluminium and rubber were placed in contact with the growth, and a dose of 3,500 mg.h. given. This removed the agonizing pain from which the patient suffered, but she died within a week of the radium treatment.

19. *Carcinoma* of the floor of the mouth in a man of 70, a patient of Mr. Miles. Inoperable and unsuitable for radium treatment.

20. *Recurrent sarcoma* of the femur in a female of 23, recommended by Professor Alexis Thomson. After amputation above the knee joint two tubes of radium were inserted and a prophylactic dose of 3,360 mg.h. was given. Eight months later her doctor reported that she was going on very well indeed.

21. *Recurrent scirrhus* in a female of 70, recommended by Dr. Scott Carmichael. The first operation nineteen months earlier; steady pain since. Second operation June 26th, 1914, when a lump was removed and a tube of radium inserted as a prophylactic. Dose 1,440 mg.h., aluminium screen. On being asked to report herself in January, 1915, the patient wrote to say that she was too ill to attend.

22. *Malignant enlargement* of the cervical glands on both sides in a male. Considered unsuitable for radium treatment.

23. *Epithelioma* of the upper lip, invading the mucous membrane, in a male of 58, recommended by Dr. Porter. Taken to see Mr. Cathcart, who recommended operation.

24. *Epithelioma* of the left tonsil of eight months' duration in a male, aged 41, recommended by Mr. Cathcart. Cervical glands enlarged. Twenty milligrams of radium in a capsule were held by the patient against the affected area daily, screened by aluminium, until a dose of 1,065 mg.h. had been given. Considerable sloughing followed, but no improvement of any consequence. The patient was referred back to Mr. Cathcart.

25. *Recurrent epithelioma* of the upper jaw in a patient, aged 46, recommended by Mr. Hodsdon. Two years ago first operation. Now a hard mass growing in a cavity above his dental plate. By means of some radium attached to the end of a wire which the patient held against the growth, a dose of 600 mg.h. was administered. Screen aluminium. The patient ceased to attend.

26. *Paraffin epithelioma* of the right hand in a man of 57, recommended by Dr. Steven. Advanced case. The patient was recommended to Mr. Wade for advice. An operation was advised.

27. *Recurrent periosteal sarcoma* of the left knee. Male, aged 23, recommended by Professor Alexis Thomson. Previous operation four years earlier. Now there is a swelling the size of a small egg, which Professor Thomson excised, and at the same time inserted 20 mg. of radium in aluminium. A dose of 2,880 mg.h. was administered. Six months later this doctor wrote to say that there was no recurrence, and that the leg was regaining strength.

28. *Periosteal sarcoma* of the lower end of the femur in a boy, aged 13. The parents refused operation. Duration five months, immobility, pain, and swelling. Greatest circumference of knee 13 in. On September 22nd, 1914, Mr. Hodsdon made an incision, and inserted 30 mg., contained in two aluminium tubes, into the swelling. Blood gushed from the growth as though it were an aneurysm. Radium, shielded by silver 1 mm. in thickness, was also applied externally. The position of the internal tubes and of the external capsules was shifted

from time to time. A total dose of 8,760 mg.h. was given. The boy was sent home. In two months' time, when he returned, it was observed that the swelling had diminished in size, the pain had disappeared, the part was less tender, and he could move it more freely. It had been growing rapidly. By a fresh incision, a tube was pushed down deeply, so as to be in contact with the bone. The part incised scarcely bled at all, and the tissues had become hard and fibrous, making it difficult to introduce the tube. A dose of 3,840 mg.h. was administered. The knee now became more swollen and tender, and the temperature rose. It was evident that the contact of the radium tube with the diseased bone was setting up a severe reaction. The boy shortly afterwards returned home. Six months later his doctor wrote to say that the right lung was affected and that the patient was sinking. The knee remained *in statu quo*, but was discharging pus from the cavity in which the tube had lain. The radium appeared to have arrested the local growth, but had not prevented a metastasis.

29. *Epithelioma* following lupus erythematosus and excessive X-ray treatment affecting the chin in a woman of 67, recommended by Dr. Gardiner. Case unsuitable for radium treatment.

30. *Epithelioma* of the vulva in a patient aged 61, recommended by Dr. Barbour. Case unsuitable for radium treatment except after an operation.

31. *Recurrent metastatic sarcoma* of right side of chest in a male of 35, recommended by Sir Robert Philip. Case unsuitable for radium treatment.

32. *Exophthalmic goitre* in a female of 28, recommended by Professor Gulland. Swelling of neck began in August, 1913, but the patient had been getting weaker before then. On admission, tachycardia (140), marked exophthalmos, tremulous, sweating, glycosuria. In March, 1914, the patient was given, by external application through silver 1 mm. thick, a dose of 360 mg.h. to the thyroid. On April 24th, 1914, the patient returned much better. Gave her a dose of 400 mg.h. On September 14th the pulse was 80, exophthalmos less, better in every way. Gave her a dose of 540 mg.h. On October 17th, 1914, gave her a dose of 400 mg.h. On December 23rd, 1914, the patient returned practically restored to health; pulse 70, no exophthalmos, thyroid cannot be palpated. Professor Gulland writes in reference to this and another case: "This case had a considerable number of applications at long intervals, and has immensely benefited thereby. She has, in fact, within a year returned to normal—an unusually good result. The second case has had only one application, and naturally did not do so well, though she also greatly improved."

33. *Exophthalmic goitre* in a girl of 27, recommended by Dr. Boyd. Duration three years. Breathlessness, nervousness, tremor of hands, pulse 120, thyroid enlarged, exophthalmos slight. This patient was given a total dose of 1,750 mg.h., administered as in the last case. On January 15th, 1915, Dr. Boyd wrote: "The patient seems to have benefited very much from radium, and I think a second dose would be very desirable."

34. *Exophthalmic goitre* in a woman of 32, recommended by Professor Gulland. A mild case of three months' duration. Slight exophthalmos, weakness, nervousness, palpitation, oedema, thyroid slightly enlarged. Medicinal treatment so far unavailing. A dose of 600 mg.h. administered externally as in the last case. This is the second patient referred to in Professor Gulland's letter, in which he described her as being greatly improved. The other three cases of exophthalmic goitre

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were only given treatment at the end of October, and they have not yet returned to report themselves.

Otosclerosis.—Two cases of otosclerosis and one of middle-ear deafness were treated with radium during the year. They are as follows:

35. A female, aged 52, recommended by Dr. J. S. Fraser. Deaf for twenty-five years, and regarded as hopeless. Dr. Fraser writes: "The raised voice before treatment could only be heard at 6 in. in both ears. After six applications of radium (dose 106 mg.h.) there was no improvement, and the patient stated that the noises had been worse. The raised voice was only heard at 4 in. in the ear which had been treated. This was a case of advanced otosclerosis."

36. Early otosclerosis in a female, aged 22, recommended by Dr. J. S. Fraser, who writes regarding her as follows: "She had been slightly deaf since childhood. Before radium treatment the low voice was heard at 1 ft. in the right ear. Radium treatment was commenced in February, 1914. I saw the patient again in May, after she had had a dose of 125 mg.h. of radium, and was suffering from a considerable amount of dermatitis of the external meatus on the right side, probably due to the radium. I saw her for the last time on November 6th, 1914, and found that the right meatus had quite healed. The hearing was about the same as before—namely, low voice at 1 ft."

37. Case of middle-ear deafness in a female of 45, recommended by Dr. J. S. Fraser, who writes as follows: "Patient had been deaf for ten months and complained of noises in the ears. Before radium treatment the raised voice was heard at 1 ft. by the left ear. After a dose of 55 mg.h. she stated that the noises were not so bad as before. The voice was heard at about 18 in. by the left ear. I do not think that the difference between 1 ft. (before treatment) and 18 in. (after treatment) is of any importance, as a small difference in hearing like this might easily be due to the room being more quiet or to the voice used being rather louder. In conclusion, I am afraid we must report that these cases of chronic progressive middle-ear deafness have not benefited from radium treatment, but this is only to be expected."

38. *Naevus* of the scalp in an infant 1 year old, recommended by Mr. Cotterill. Had been treated by injections of carbolic acid and glycerine. There was a scab in the centre and a raised red ring around. A dose of 115 mg.h. was sufficient to cure this condition.

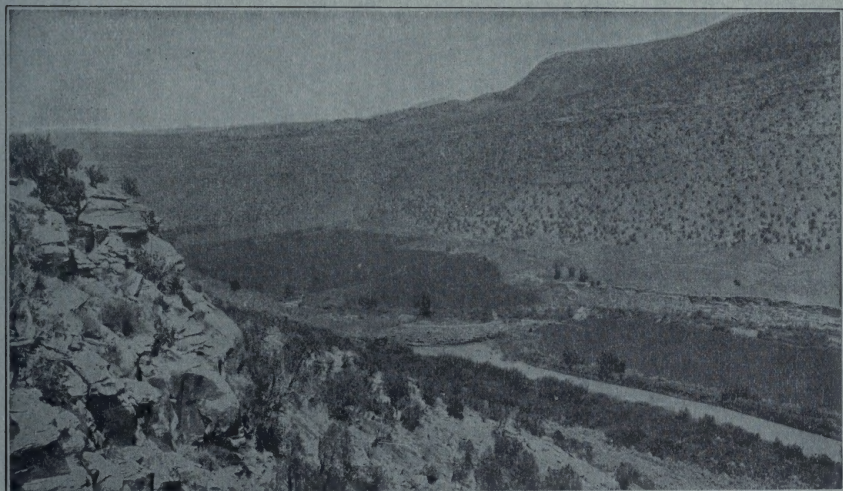
39. *Paget's disease* in a female aged 72, recommended by Mr. Miles. To right of nipple is a well defined crescentic area, red, slightly elevated, and hard. Glands not palpable. Nipple normal. A dose of 1,200 mg.h. was administered, guarded by silver and cork, so as to spread the effect. The patient has not reappeared for treatment.

40. *Warty tumour* in a girl aged 18, recommended by Dr. Ogilvie. Duration about two years. Has had nitric acid and other applications without benefit. On the left cheek is a wart the size of a threepenny piece considerably elevated above the surface. Radium treatment begun on March 24th, 1914, and a dose of 58 mg.h. administered. On June 2nd, 1914, the wart was found to have disappeared and the skin to be practically normal.

41. *Leucoplakia*. As this case was only admitted for treatment in December, 1914, it is too early to make any report.

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